

Efficacy and Complications of Surgery for Crohn's Disease

Robert T. Lewis, MD, and David J. Maron, MD

Dr. Maron is a staff surgeon and Associate Director of the Colorectal Surgery Residency program at the Cleveland Clinic Florida in Weston, Florida. Dr. Lewis is a resident in the Department of Surgery in the University of Pennsylvania Health System in Philadelphia, Pennsylvania.

Address correspondence to:

Dr. David J. Maron
Department of Colorectal Surgery
Cleveland Clinic Florida
2950 Cleveland Clinic Boulevard
Weston, FL 33331;
E-mail: marond@ccf.org

Abstract: Patients with Crohn's disease commonly undergo surgery during their lifetime. Indications for surgical intervention include obstruction, intra-abdominal or perianal abscess, enterocutaneous fistulas, and complex perianal disease. As medical therapies continue to improve, it is important that surgical therapies are chosen carefully. This is particularly important in the treatment of perianal fistulas; combined surgical and medical therapy offer the best chance for success. In the treatment of small-bowel disease, bowel preservation is key. For the repair of short strictures, endoscopic dilatation is the preferred method when accessible; strictureplasty has been shown to be safe and effective for increasingly longer segments of disease. Intra-abdominal abscesses should be drained percutaneously, if possible. In the presence of colonic disease, segmental resection is recommended. Unfortunately, refractory disease still frequently requires complete proctectomy and permanent diversion.

Between 70% and 90% of patients with Crohn's disease will require surgery during their lifetime,^{1,2} even those who first present with a nonfistulizing, nonpenetrating phenotype,³ and as many as 39% will require repeated surgery.⁴ The percentages of patients with obstructing phenotypes and of penetrating phenotypes are approximately even,⁵ and no genotype has been reliably linked with phenotypic presentation or progression⁶ (including the *CARD15* gene⁷). Indications for surgery include complications from strictures, intra-abdominal and perianal fistulas, intestinal perforation, intra-abdominal abscess, gastrointestinal bleeding, malignancy, and growth restriction in children.⁸

Estimates of the prevalence of perianal involvement in Crohn's disease have varied greatly, but the most recent population-based series demonstrate that anorectal involvement is seen in 14–38% of Crohn's disease patients,^{9–11} with isolated perianal disease seen in only 5%.¹² In patients with ileocolonic Crohn's disease, only 15% will develop fistulas, though fistulas occur in 92% of patients with colonic Crohn's disease and rectal involvement.¹¹ In most cases, bowel involvement antecedes perianal disease.¹³ There does not appear to be a predilection for age, with 13–62% of children and

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adolescents experiencing perianal manifestations.^{10,14,15} A study of 1,126 patients with Crohn's disease found that whites more commonly have proximal disease (odds ratio [OR], 1.8) and are less likely than Hispanics or African Americans to have perianal manifestations (OR, 0.58).¹⁶ The presence of anal disease is associated with a more disabling natural history,¹⁷ with more frequent extraintestinal manifestations¹⁸ and increased steroid resistance.¹⁹ The disease is recurrent, with 35–59% of patients relapsing within 2 years.²⁰

Surgery for Crohn's disease is not curative. Although some debate exists as to whether early intervention may be beneficial in select cases, excess intervention can be harmful,^{4,21} making the timing of interventions require considerable judgment. As medical therapy continues to improve, this decision is increasingly shared between gastroenterologists and surgeons.

Intestinal Disease

Strictureing Disease

Patients with stricturing Crohn's disease are at risk for the development of intestinal obstruction. Acute obstruction is often due to a plug of indigestible fiber that is ingested or to inflammation at a site of active disease, and can be managed conservatively with a low residual diet and medical therapy in the majority of cases.²² Approximately 30% of Crohn's patients have disease limited to the ileum, and surgery can offer these patients durable remission. One half of Crohn's patients, however, will have multifocal ileocolonic disease, and these patients are almost 3 times as likely to require further surgery.²³ It is, therefore, important to understand the patient's extent of disease at presentation and to rely upon methods increasingly focused on bowel preservation in patients with multiple strictures or recurrent disease. With evidence that extensive resection is potentially harmful,²⁴ methods that preserve the bowel have become more popular, including strictureplasty techniques and endoscopic balloon dilatation.

Endoscopic dilatation may be an attractive nonoperative option in the treatment of Crohn's strictures. A recent quantitative review²⁵ demonstrated that the endoscopic approach was technically successful in 86% of patients, with a major complication rate of 2–18%. In successful patients, only 42% required surgical intervention an average of 15 months after dilatation. Of note, although these results are promising, the majority of these reviewed series examined postoperative strictures, and short-segment disease (<4 cm) was the only predictor of long-term benefit. With a risk of perforated viscus, endoscopic dilatation should not be attempted without the availability of a surgical team.²⁶

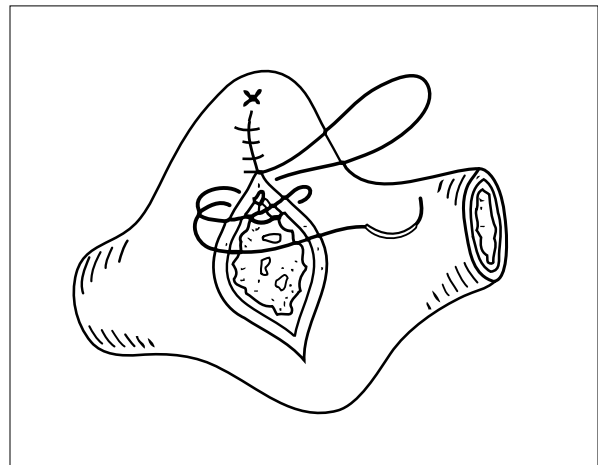


Figure 1. Heineke-Mikulicz strictureplasty.

Reproduced from Kumar D, Alexander-Williams J. *Crohn's Disease and Ulcerative Colitis: Surgical Management*. London, United Kingdom: Springer; 1993:89-101.

First described in the 1970s,²⁷ strictureplasty is recommended in cases where bowel length preservation is critical (patients with recurrent disease after small-bowel resection), in cases where resection would be extensive (diffuse small-bowel involvement), or in cases with a single site of fibrotic, inactive disease.²⁸ The recommended length of strictured intestine that can be repaired varies between 10 cm and 25 cm,^{26,29,30} though Michelassi and colleagues³¹ and Poggioli and coworkers³² have described successful strategies for segments up to 90 cm. The Heineke-Mikulicz strictureplasty is the most commonly performed technique and is useful in strictures under 10 cm³³ (Figure 1). Strictureplasty should be avoided in colonic strictures secondary to Crohn's disease, though a study of 29 patients found colonic strictureplasty to be safe.³⁴

Yamamoto and associates³⁵ pooled data on 1,112 patients who underwent 3,259 strictureplasties and found a morbidity rate of 13%, with fistula and abscess being the leading postoperative complications, followed by postoperative gastrointestinal bleeding and wound infection. Overall, 26% of patients experienced recrudescence of disease, usually within 5 years,³⁰ and recurrence at another site in 25%.³⁵

Small-bowel resection is the most commonly performed operation for Crohn's disease.³⁶ For patients with limited disease, early resection may be the best option. In a study of 36 patients with ileal Crohn's disease diagnosed during appendectomy, Weston and associates³⁷ found that 92% of patients who did not undergo ileocelectomy required additional surgery within 1 year, whereas only

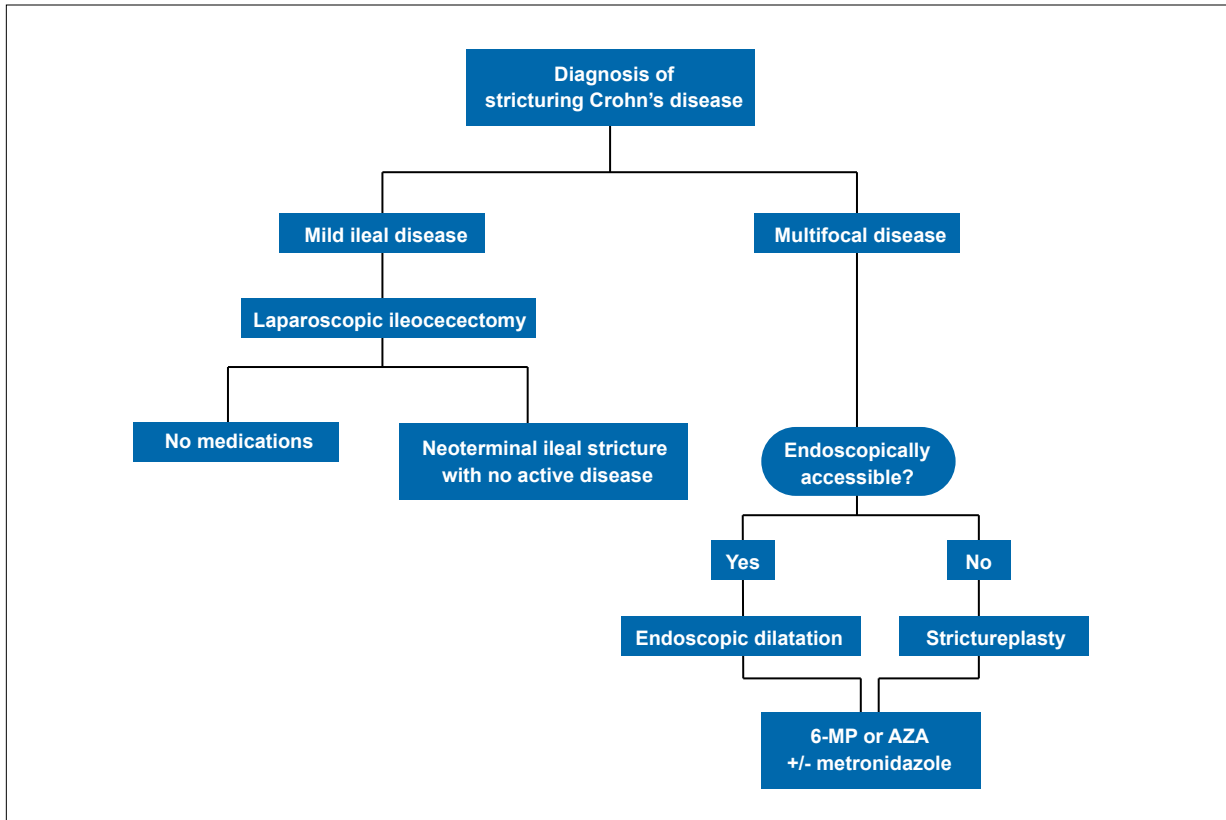


Figure 2. Treatment algorithm for stricturing Crohn's disease.

6-MP=6-mercaptopurine; AZA=azathioprine.

Modified from Cho SM, et al.⁴⁷

50% of the patients who underwent immediate ileocelectomy required additional surgery, with a mean follow-up of 12 years.

Indications for a small-bowel resection include chronic obstructive symptoms, failure of medical therapy, perforation or abscess, and dysplasia or malignancy. Only the portion of small bowel grossly involved should be resected, with margins of 2 cm or less. A randomized controlled trial by Fazio and coworkers³⁸ of 152 patients showed no benefit with margins between 2 cm and 12 cm, and leaving behind histologically active disease did not appear to effect recurrence.³⁹

Minimally invasive techniques have recently been employed in the treatment of Crohn's disease. Investigators have examined whether a laparoscopic or open approach for performing an uncomplicated small-bowel resection is preferable. Two randomized controlled trials totaling 120 patients undergoing ileocolic resection for Crohn's disease have been conducted. The authors found laparoscopic surgery to be equivalent⁴⁰ or superior⁴¹ to an open approach, measured by duration of hospital stay,

morbidity, and (in Maartense and associates⁴¹) overall costs. Stocchi and colleagues⁴² recently found the results reported by Milsom and coworkers⁴⁰ to be durable at 10 years, with no increased risk of recurrence or missed disease in the laparoscopic arm. Nearly all series describe an average of 30 minutes of additional operative time with a laparoscopic approach,⁴³ and many have reported conversion rates of up to 40%.⁸ Conversion to an open approach, however, does not adversely affect final outcome,⁴⁴ and the conversion rate may improve with surgeon experience.⁴⁵ Recent series have shown laparoscopic surgery to be feasible and safe even for complex, recurrent cases of Crohn's disease.⁴⁶

In summary, patients presenting with mild or moderate disease localized to the ileum may have a chance at durable remission and should be offered early surgical intervention with a small-bowel resection extirpating the diseased segment, preferably via a laparoscopic approach. Patients with strictures and no active disease at the site can be treated with either endoscopic dilatation or strictureplasty, once conservative management fails. Complex

strictureplasty is best reserved for patients with multifocal recurrent ileocolic disease, and reasonable recurrence rates can safely be obtained with longer segments of diseased bowel as surgical technique continues to improve. A treatment algorithm for patients with stricturing Crohn's disease is outlined in Figure 2.⁴⁷

Penetrating Disease

Penetrating disease can result in intra-abdominal fistulas between 2 intestinal sites involved with Crohn's disease, between involved sites and "innocent" organs, and between involved sites and the skin. Penetrating Crohn's disease can also result in intra-abdominal abscess and sepsis.

A fistula is the second most common primary indication for surgery, but it is almost always accompanied by another abnormality such as an intra-abdominal abscess or inflammatory mass.⁴⁸ Fistulas are frequently found during operations for medically refractory Crohn's disease. In a series of 639 patients undergoing surgery, 222 (34.7%) had a total of 290 fistulas, 27% of which were diagnosed perioperatively.⁴⁹

Small bowel to small bowel fistulas are often asymptomatic and do not typically require surgical intervention. Up to 40% of these patients, however, may progress to surgery within 1 year.⁵⁰ In addition to causing abdominal abscess and pain, symptomatic fistulas between the proximal small bowel and colon can bypass a large portion of the bowel, resulting in malabsorption. These fistulas should be repaired as soon as the patient's nutritional status is stabilized. Surgical treatment involves resection of the involved small bowel and either repair of the fistula target (in the event of an enterovesicular or enterovaginal fistula) or wedge resection (if the target is the large bowel).⁵¹ Some physicians have found that repaired sigmoid sites were apt to leak and therefore recommend a limited sigmoid resection.⁵² Primary anastomosis is safe, and diversion is rarely required.

Enterocutaneous fistulas can be medically managed in as many as 30% of cases,⁵³ but only if there is no associated intra-abdominal abscess.⁵⁴ Nutritional support is critical; enteral feeding is preferred, though total parenteral nutrition has also been shown to be of benefit.⁵⁵ Although the benefit of good nutrition and meticulous wound care are widely accepted, there is a lack of information regarding effective treatment with medications. Octreotide, a somatostatin analogue, has been shown to dramatically decrease the output of enterocutaneous fistulas,⁵⁶ but it does not reduce the need for surgery in Crohn's patients.⁵⁷ The ACCENT-1⁵⁸ and ACCENT-2⁵⁹ trials, which effectively used infliximab (Remicade, Centocor) for the treatment of penetrating Crohn's disease, did include 9 (of 94) and 39 (of 306) patients with abdominal enterocutaneous fistulas. As no subgroup analysis was performed on these

patients alone, it is difficult to extrapolate the success seen with perianal disease to abdominal fistulas. Another series found that, while infliximab healed perianal fistulas, it did not result in the closure of enteroenteral or enterocutaneous fistulas, which still required surgery.⁶⁰ Therefore, although infliximab therapy can be attempted, after a trial of at least 6 weeks, surgical intervention should be considered.⁶¹

Approximately 25% of Crohn's patients will develop an intra-abdominal abscess during their lifetime, often in association with a fistulous tract.⁶² In these cases, percutaneous drainage should be attempted whenever possible, as successful drainage can successfully avoid surgery in as many as two thirds of patients.⁶³ Up to half of abscesses will recur, though this risk is less when surgically drained.⁶⁴ In contrast, when an abscess is diagnosed intraoperatively (as occurs in 50% of cases),⁴⁹ involved bowel should be resected. A stoma is often necessary to protect the anastomosis.⁶⁵

Other Surgical Indications

Gastrointestinal hemorrhage is a rare complication of Crohn's disease and accounts for only 1% of operations. Given the desire to minimize resection of uninvolved small bowel, preoperative localization is of paramount importance. Angiography can be very helpful in preoperatively localizing the disease if the patient is actively bleeding.⁶⁶

Although adenocarcinoma of the colon is slightly more common in patients with Crohn's disease than in the general population,⁶⁷ the risk of small-bowel carcinoma is 60-fold higher.⁶⁸ The risk is particularly high in patients with surgically bypassed segments,⁶⁹ a practice that has fallen out of favor.⁷⁰ Surgical resection of all involved segments and the nodal basin is recommended, but outcomes are usually poor, as the disease is often advanced at the time of diagnosis.^{69,71}

Postoperative Recurrence

Endoscopic recurrence occurs in 70–90% of patients⁷² within as little as 1 week after surgery and becomes symptomatic in 60% of patients within 10 years.⁷³ One third of patients will require repeat surgical intervention.⁶⁹ Smokers have a 2.5-fold higher risk of requiring additional surgery⁷⁴ and having a family history of Crohn's disease increases surgical recurrence 2-fold.⁷⁵ The gold standard in surveillance is colonoscopy, which is recommended annually or biannually. The standard therapy to extend clinical remission has been treatment with immunomodulators, including 6-mercaptopurine and azathioprine,⁴⁷ though recent data, including a randomized controlled trial in 24 patients,⁷⁶ have shown a 90% reduction of endoscopic recurrence at 1 year in patients receiving infliximab therapy.

Perianal Disease

Perianal Fistula

Abscess and fistula are the most common presentations of anorectal Crohn's disease. Twenty-six percent of patients will present with an abscess, and an additional 29% will present with a fistula.⁷⁷ A thorough examination must be performed before treatment is initiated, with special attention given to establishing the presence or absence of rectal inflammation. Any collection should be immediately drained. Beyond this point, treatment options for fistulas become extremely varied. Fistulas should be categorized as simple (defined as superficial, inter-, or trans-sphincteric fistulas below the dentate line, with a single opening and no anorectal stricture or abscess) or complex (defined as a trans-, supra-, or extrasphincteric fistula above the dentate line; a fistula with multiple external openings, an associated abscess, or stricture; or a rectovaginal fistula).¹⁰ Combined medical and surgical approaches offer the best chance for success.⁷⁸⁻⁸⁰

An examination under anesthesia (EUA) has traditionally been considered the gold standard for diagnosis of Crohn's-related fistula, but a prospective study by Schwartz and coworkers⁸¹ in 34 patients found that EUA had an accuracy of only 90%, based upon a composite gold standard derived from EUA, anal endoscopic ultrasound (EUS), and pelvic magnetic resonance imaging (MRI). This same study found that accuracy was 100% when any 2 of these 3 procedures were performed.

Pelvic MRI is the preferred imaging modality in the classification of fistulizing perianal disease and has been shown to have an accuracy of 90%^{82,83} when classifying fistulas and 97% when delineating complex abscesses, though endoanal ultrasound is only slightly inferior.^{81,83,84} Surgical management can be altered in as many as 40% of Crohn's patients with the addition of MRI to EUA.^{85,86}

Perianal abscess presents with pain, swelling, and fluctuation on rectal examination, and is thought to form by extension of a cryptoglandular infection or by obstruction of a perianal fistula. Abscesses can develop in any plane (superficial, intersphincteric, ischiorectal, or supralelevator); however, regardless of location, they require prompt surgical incision and drainage and treatment of systemic symptoms with broad-spectrum antibiotics.^{10,87} Many physicians advocate placing a drain or partially dividing sphincters to facilitate drainage, but these devices have not been shown to improve outcomes.^{88,89} EUS has been used with success to guide the incision of deep or complex abscesses.⁹⁰

In the presence of a fistula, a noncutting seton made of an inert material can be placed to prevent recurrence of abscess and to facilitate drainage, with healing or improvement seen in 79–100% of patients.⁹¹⁻⁹⁶ Setons

can be left in place long term without consequence; removal without definitive therapy results in recurrence in 20–80% of patients.^{94,97,98} In patients with persistent sepsis, a diverting stoma can be effective in up to 80% of patients, but it is rarely reversed—in only 4 of 18 (22%) patients in one study.⁹⁹

Once a fistula is characterized and any concomitant abscess controlled, combined definitive medical and surgical therapy should be initiated. Antibiotics have been shown to be effective as a bridge to immunosuppressive therapy,¹⁰⁰ with 70–95% of patients experiencing a positive clinical response within 6–8 weeks^{101,102} and a worsening of symptoms when the antibiotics are discontinued or decreased.¹⁰³ Fewer than 50% of patients, however, experience healing of the fistula on antibiotic therapy alone, and the majority of cases will recur if antibiotics are withdrawn.¹⁰⁴

More definitive medical therapy requires immunosuppression. A meta-analysis of 5 randomized controlled trials examined the efficacy of 6-mercaptopurine and azathioprine and showed that, in these 70 patients, 54% of treated patients experienced fistula healing versus only 21% of controls.¹⁰⁵ Cyclosporine has excellent, rapid effect in up to 83% of patients when given intravenously,^{106,107} but the effect is not durable when patients are transitioned to oral medication or when therapy is discontinued.¹⁰⁸ Tacrolimus has also shown efficacy in a randomized controlled trial, resulting in at least a 50% improvement in 43% of patients versus 8% in the placebo arm.¹⁰⁹

Infliximab has proven to be particularly effective in the treatment of perianal fistulas in patients with Crohn's disease. The ACCENT-1 trial of 92 patients showed efficacy with induction therapy: 68% of patients treated with infliximab had at least a 50% improvement versus 26% with placebo.⁵⁸ The ACCENT-2 trial documented longer time to recurrence of fistulas with infliximab maintenance therapy (40 weeks vs 14 weeks for placebo).⁵⁹ In addition, treatment with infliximab resulted in less need for surgery and fewer hospitalizations.⁵⁹ Interestingly, rectovaginal fistulas have a poorer response to infliximab therapy—only 14–30% heal compared to 46–78% of other perianal fistulas.^{58,110,111} The anti-tumor necrosis factor (TNF) antibody adalimumab (Humira, Abbott) has a similar safety profile to infliximab¹¹² and had similar efficacy in a randomized controlled trial (the CHARM trial). Complete fistula closure at 1 year was seen in 39% of treated patients compared to 13% of the placebo arm.¹¹³ These results have been shown to be durable at 2 years.¹¹⁴

Fistulotomy, or the opening of the fistula tract via division of overlying tissues, offers the best chance for definitive treatment of perianal fistulas. Several series have examined the effect of fistulotomy in patients with low perianal fistula, with most reporting healing

rates between 80% and 100%.¹⁰ When the investigators specifically noted the absence of rectal inflammation, results improved further, with healing achieved in 22 of 24 (92%) patients and recurrence in only 4 of 24 (17%) patients.^{89,115,116} Conversely, a study that specifically noted active proctocolitis at the time of surgery documented a healing rate of only 27% of fistulas.¹¹⁷

Much of the concern regarding operating on patients with anorectal Crohn's disease has been due to the possibility of repeat iatrogenic injury to the sphincter muscle.¹¹⁸ Newer therapies using fibrin glue and anal fistula plugs have been developed that do not require any division of muscle.¹¹⁹ Success using fibrin glue, however, has been mixed, with 60–78% of simple fistulas healed, but only 14–50% of complex fistulas healed in the general population¹²⁰ and only 31–57% of fistulas in patients with Crohn's disease.^{121,122} In contrast, initial outcomes using the collagen anal fistula plug have been more promising; a prospective study of 20 patients found that the plug was able to close 80% of fistulas in patients with Crohn's disease¹²³ and 85% of fistulas in the general population.¹²⁴ Other researchers, however, have shown poor outcomes (20% long-term healing) in patients with Crohn's disease and complex fistulas.¹²⁵

Once a simple fistula is diagnosed (and there is no rectal inflammation), it appears safe to perform either a fistulotomy or placement of an anal fistula plug while initiating medical therapy. In the setting of proctitis, outcomes are not as good, and medical therapy with the placement of a seton, anticipating possible fistulotomy should proctitis resolve in 6–8 weeks, may offer the best chance for success.

Complex fistulas are defined as high perianal fistulas or fistulas with branched tracts, associated abscess, or multiple external openings.¹⁰ First-line therapy is infliximab, which, as mentioned above, has had excellent results in this population in multiple randomized controlled trials,^{58,59} usually with the addition of immunosuppression. Adjunct surgical therapy, with temporary placement of a loose seton at the time of induction, can be helpful in 47–67% of cases.^{79,126}

Fistulotomy is not recommended for complex fistulas, as previous series have found nonhealing and incontinence. As many as 40–60% of patients may eventually require proctectomy.^{117,127} In the absence of proctitis, however, a transanal advancement flap may be a good option. In this procedure, the internal fistula opening is excised and the mucosa, submucosa, and circular muscle are mobilized as an island and placed over the fistula tract. Investigators have demonstrated healing in as many as 89% of patients, but a disappointing rate of recurrence, up to 50%.^{128–130} A transanal sleeve advancement flap, in which the entire rectal mucosa is advanced over the

internal fistula opening, is another alternative and has resulted in healing in 62% of cases, with a recurrence rate of 38%.¹³¹ Finally, a loose seton can be left indefinitely without significant effect on continence.¹³²

Crohn's disease is the second most common cause of rectovaginal fistula.¹³³ The initial treatment does not vary from that of other complicated fistulas, though, as noted above, infliximab does not have the same response rate in this population.¹³⁴ Rectal advancement flaps are effective, with 54–71% healing,^{135,136} and similar results have been seen using rectal sleeve advancement flaps.^{135,137} Although most physicians advocate the use of rectal flaps, as the rectum is the high pressure side of the fistula, one series has demonstrated 92% healing in 14 patients treated with a vaginal advancement flap.¹³⁸ In recurrent cases, repeating the flap can have some success (14% of cases in one series).¹³⁵

Diversion and Proctectomy

A diverting ileostomy or, rarely, a colostomy can be helpful in severe perianal disease, with permanent stoma required in up to 37–49%. Risk factors include colon involvement, anal stricture, incontinence, and complex perianal fistulas.^{139,140}

Temporary diversion is indicated when perianal disease is extremely extensive or progressive despite drainage of abscess and maximal medical therapy.¹⁴¹ Diversion may help to create a more favorable environment for complex perianal repairs. Yamamoto and associates¹⁴² found that although 25 of 31 (81%) patients experienced early remission, 17 (55%) relapsed, most required eventual proctectomy, and only 3 (10%) were able to have the stoma reversed. Permanent diversion, however, can improve quality of life; Kasperek and colleagues¹⁴³ found that only 44% of diverted patients complained of Crohn's disease symptoms compared to 79% of undiverted patients.

Proctectomy may be indicated in patients who fail medical and surgical therapy, or in the presence of aggressive and unrelenting rectal disease. Resection of the rectum with permanent colostomy is required in 10–20% of cases.¹⁰ Unfortunately, proctectomy can be complicated by poor wound healing and perineal sinus formation in up to 25–50% of patients.^{144,145} A gracilis or rectus flap¹⁴⁶ can be used to help combat these complications.

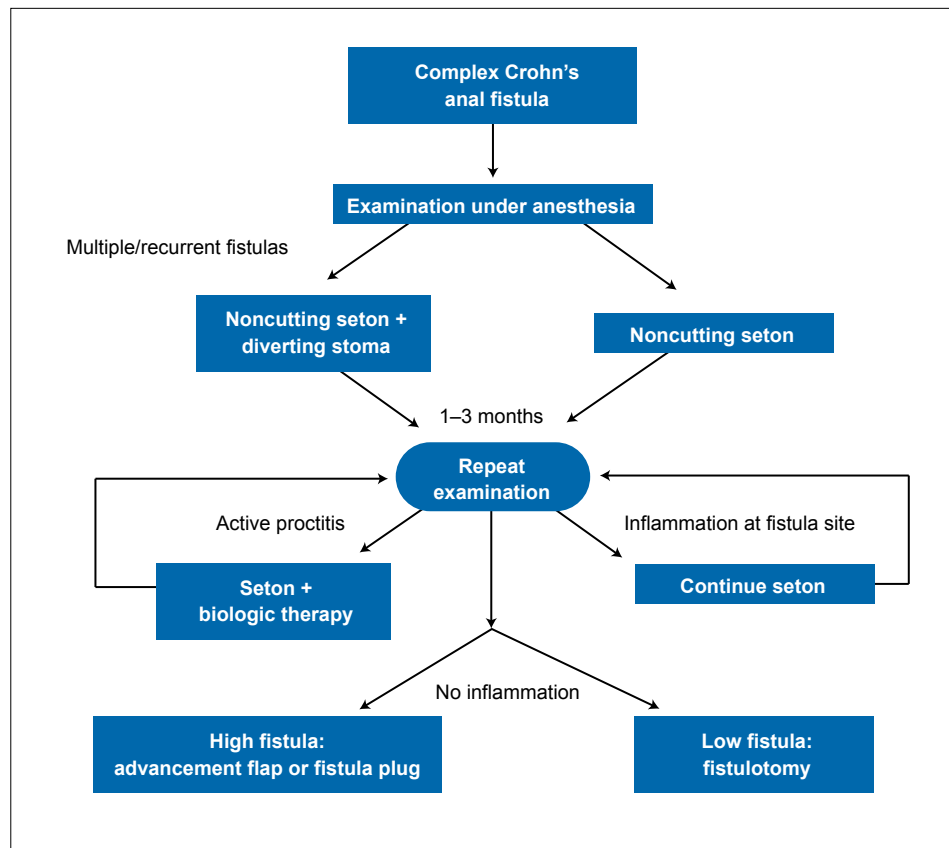
An algorithm for the approach to perianal disease management is shown in Figure 3.¹⁴⁷

Summary

Crohn's disease is a chronic incurable relapsing disease with a large variability in clinical presentation and is caused by idiopathic full thickness inflammation at any point in the gastrointestinal tract. Nearly all patients

Figure 3. Approach to management of Crohn's perianal fistula.

Reproduced from van der Hagen SJ, et al.¹⁴⁷



require surgery during their lifetime for palliation of symptoms and complications of the illness. However, in the last 2 decades, medical treatments have advanced considerably, particularly with the development of anti-TNF therapeutics such as infliximab.

There is some evidence that mild ileal disease benefits from early excision, though recurrent or multifocal disease should be treated using techniques that preserve small-bowel length and function. Endoscopic dilatation of accessible lesions (<4 cm in length) or strictureplasty of lesions less than 25 cm in size (and, in rare situations, up to 90 cm) are increasingly safe and effective. Intra-abdominal abscesses should be drained percutaneously when possible. For perianal fistulas, combined medical therapy with a noncutting seton followed by judicious fistulotomy or (when fistulotomy is not possible) advancement flaps has been shown to be most effective in treatment of complex perianal disease. Despite all these advances, refractory cases, particularly with proctitis, often require proctectomy and permanent diversion.

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